

10/562950

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1A328 Rec'd PCT/PTO 28 DEC 2005

I, VIVIEN IRENE COULSON, declare:

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 96 Langley Road, Watford, Hertfordshire, WD17 4PJ;
2. That I am well acquainted with the French and English languages;
3. That the attached is a true translation into the English language of the certified copy of European Patent Application No. 03291600.9 filed 30 June 2003;
4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

Declared this

6<sup>th</sup>

day of

October 2005

*V.I. Coulson*

V.I. COULSON

**10/562950**

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**European  
Patent Office**

## **Certificate**

The attached documents are exact  
copies of the European patent  
application described on the following  
page, as originally filed.

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**Patent application No.**

03291600.9

For the President of the  
European Patent Office

[signature]

**R C van Dijk**



European  
Patent Office

Application no.: 03291600.9

Date of filing: 30.06.03

Applicant(s):

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FRANCE

Title of the invention:  
(If no title is shown please refer to the description.)

New process for the synthesis of perindopril and its pharmaceutically acceptable salts

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State/Date/File no.:

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SE SI SK TR LI

**10/562950**

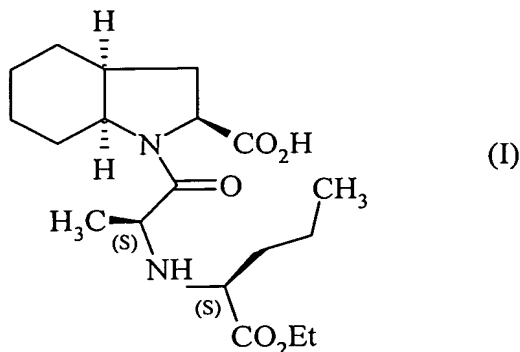
**IAP20 Rec'd PCT/PTO 23 DEC 2005**

**NEW PROCESS FOR THE SYNTHESIS OF PERINDOPRIL  
AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS**

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**INVENTORS :      Thierry DUBUFFET  
                         Jean-Pierre LECOUBE**

The present invention relates to a process for the industrial synthesis of perindopril of formula (I) :



and its pharmaceutically acceptable salts.

5 Perindopril and its pharmaceutically acceptable salts, and more especially its tert-butylamine salt, have valuable pharmacological properties.

Their principal property is that of inhibiting angiotensin I converting enzyme (or kininase II), which allows, on the one hand, prevention of the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the  
 10 other hand, prevention of the degradation of bradykinin (a vasodilator) to an inactive peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular diseases, more especially in arterial hypertension and heart failure.

Perindopril, its preparation and its use in therapeutics have been described in European  
 15 patent specification EP 0 049 658.

In view of the pharmaceutical value of this compound, it has been important to be able to obtain it by an effective industrial synthesis process, readily transposable to an industrial scale, that leads to perindopril in a good yield and with excellent purity starting from reasonably priced starting materials.

20 Patent specification EP 0 308 341 describes the industrial synthesis of perindopril by the peptide-type coupling of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid benzyl ester with

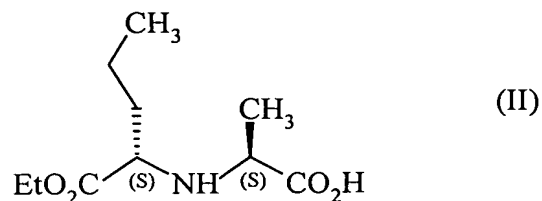
N-[(S)-1-carboxybutyl]-(S)-alanine ethyl ester, followed by deprotection of the carboxylic group of the heterocycle by catalytic hydrogenation.

5 That process has the advantage of yielding perindopril in a good yield from starting materials for which industrial synthesis has already been described.

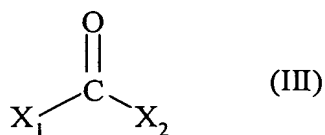
However, it also has drawbacks associated with the use of dicyclohexylcarbodiimide in the coupling step : the formation of coupling impurities, and of dicyclohexylurea, a by-product which is difficult to remove.

The Applicant has now developed a new process for the industrial synthesis of perindopril that avoids the formation of those secondary products.

More specifically, the present invention relates to a process for the industrial synthesis of perindopril and its pharmaceutically acceptable salts which is characterised in that the compound of formula (II) :

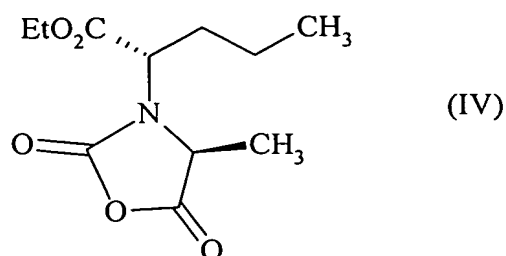


is reacted with a compound of formula (III) :

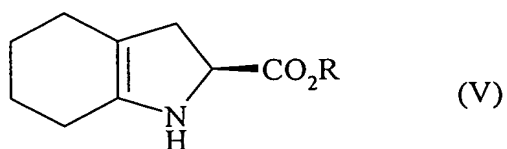


wherein X<sub>1</sub> and X<sub>2</sub>, which may be identical or different, each represents a leaving group, to yield the compound of formula (IV) :

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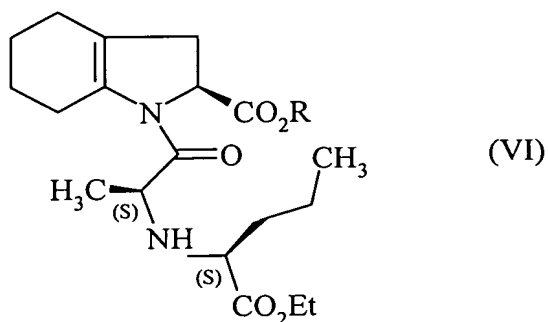
which is reacted with a compound of formula (V) :



wherein R represents a hydrogen atom or a benzyl or linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

or an addition salt thereof with a mineral or organic acid,

to yield, after isolation, a compound of formula (VI) :



wherein R is as defined hereinbefore,

which is hydrogenated in the presence of a catalyst such as, for example, palladium, platinum, rhodium or nickel,

under a hydrogen pressure of from 1 to 30 bars, preferably from 1 to 10 bars, to yield, after deprotection where necessary of the acid function, perindopril of formula (I) which is converted, if desired, to a pharmaceutically acceptable salt such as the tert-butylamine salt.

Appropriate leaving groups  $X_1$  and  $X_2$  that may be mentioned, without implying any limitation, include the halogen atoms and the groups tosylate, mesylate, linear or branched  $(C_1-C_6)$ alkoxy, linear or branched  $(C_1-C_6)$ alkylthio, imidazolyl, benzimidazolyl, tetrazolyl, benzotetrazolyl, linear or branched trihalo- $(C_1-C_6)$ alkyl, linear or branched trihalo- $(C_1-C_6)$ alkoxy, and succinimidylloxy.

Preferred leaving groups  $X_1$  and  $X_2$  that may be mentioned include the chlorine atom and the imidazolyl and trichloromethoxy groups.

The Example below illustrates the invention but does not limit it in any way.

**EXAMPLE :** (2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]-propionyl]octahydro-1H-indole-2-carboxylic acid tert-butylamine salt

Step A : Ethyl (2S)-2-[(4S)-4-methyl-2,5-dioxo-1,3-oxazolidin-3-yl]pentanoate

- 5 Introduce into a reactor, at 0°C, 200 g of N-[(S)-ethoxycarbonyl-1-butyl]-(S)-alanine, 1.5 litres of toluene, and then 184 g of 1,1'-carbonyldiimidazole, then bring the temperature of the reaction mixture to 20°C. After stirring for 1 hour at 20°C, cool the mixture to 0°C again, filter off the precipitate obtained, then evaporate the filtrate to yield the title product in a yield of 90 %.

10

Step B : (2S)-1-[(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]propionyl]-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylic acid

Introduce 200 g of (2S)-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylic acid and 1.5 litres of dichloromethane into a reactor, followed by 180 ml of triethylamine.

- 15 Subsequently, slowly add a solution of 290 g of the compound obtained in the above Step in 500 ml of dichloromethane and then stir for a further 1 hour at ambient temperature. After the addition of water, the reaction mixture is cooled to 15°C and the pH is adjusted to 4.2 by the addition of a 2N hydrochloric acid solution. Following extraction, the organic phases are washed and then evaporated to yield the expected product.



Step C : (2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]propionyl]-  
octahydro-1H-indole-2-carboxylic acid

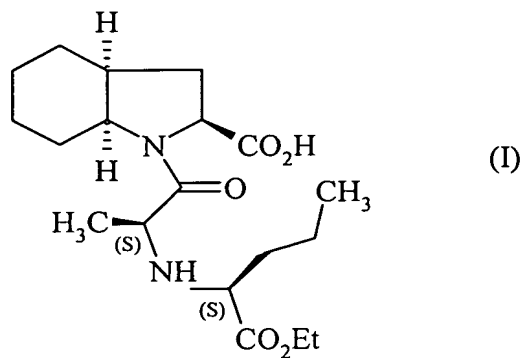
Introduce into a hydrogenation vessel 200 g of the compound obtained in the above Step in  
solution in acetic acid, and then 5 g of 10 % Pt/C. Hydrogenate under a pressure of 5 bars  
5 at ambient temperature until the theoretical amount of hydrogen has been absorbed.  
Remove the catalyst by filtration, and then cool to from 0 to 5°C and recover, by means of  
filtration, the solid obtained. Wash the cake and dry it to constant weight.

Step D : (2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]propionyl]-  
octahydro-1H-indole-2-carboxylic acid tert-butylamine salt

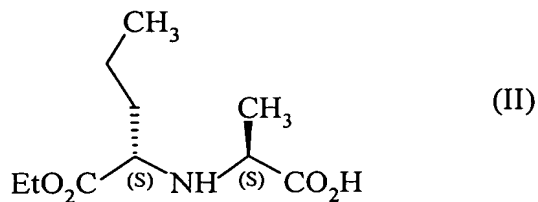
- 10 The lyophilisate obtained in the above Step (200 g) is dissolved in 2.8 litres of ethyl  
acetate, and then 40 g of tert-butylamine and 0.4 litre of ethyl acetate are added.  
The suspension obtained is then refluxed until complete dissolution occurs, and the  
solution obtained is then filtered in the heated state, and cooled, with stirring, to a  
temperature of from 15 to 20°C.
- 15 The precipitate obtained is subsequently filtered off, made into a paste again with ethyl  
acetate, dried and then crushed to yield the expected product in a yield of 95 %.

**CLAIMS**

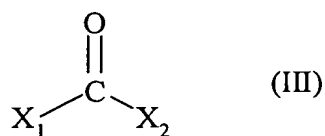
1. Process for the industrial synthesis of the compounds of formula (I) :



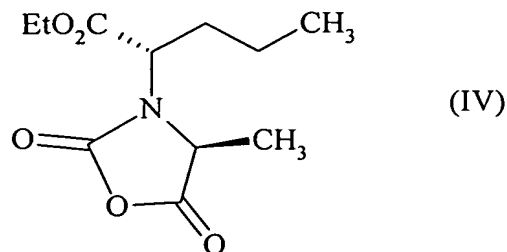
and its pharmaceutically acceptable salts,  
characterised in that the compound of formula (II) :



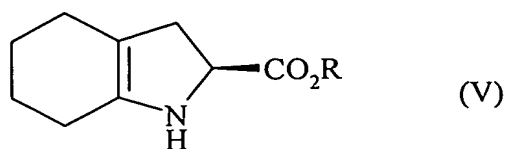
is reacted with a compound of formula (III) :



wherein X<sub>1</sub> and X<sub>2</sub>, which may be identical or different, each represents a leaving group,  
to yield the compound of formula (IV) :



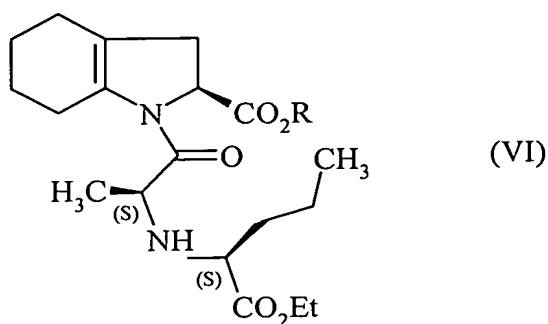
which is reacted with a compound of formula (V) :



wherein R represents a hydrogen atom or a benzyl or linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

or an addition salt thereof with a mineral or organic acid,

5 to yield, after isolation, a compound of formula (VI) :



wherein R is as defined hereinbefore,

which is hydrogenated in the presence of a catalyst such as, for example, palladium, platinum, rhodium or nickel,

10 under a hydrogen pressure of from 1 to 30 bars, to yield, after deprotection where necessary of the acid function, perindopril of formula (I) which is converted, if desired, to a pharmaceutically acceptable salt such as the tert-butylamine salt.

15 2. Synthesis process according to claim 1, characterised in that the hydrogen pressure in the hydrogenation reaction is from 1 to 10 bars.

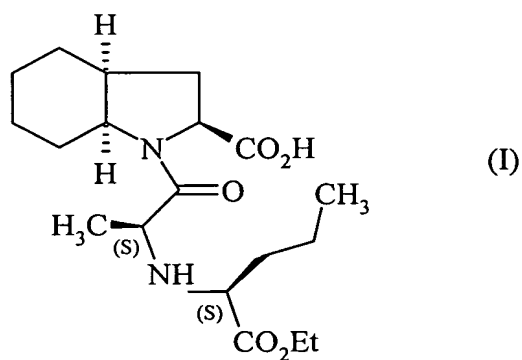
3. Synthesis process according to claim 1 or claim 2, characterised in that X<sub>1</sub> and X<sub>2</sub> each represent a chlorine atom or an imidazolyl or trichloromethoxy group.

20 4. Process according to any one of claims 1 to 3 for the synthesis of perindopril in the form of its tert-butylamine salt.

**ABSTRACT**

**NEW PROCESS FOR THE SYNTHESIS OF PERINDOPRIL  
AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS**

Process for the industrial synthesis of perindopril of formula (I) :



and its pharmaceutically acceptable salts.